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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,493	06/08/2007	Takahide Kohro	032218A	1082

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
01/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentmail@whda.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,493	KOHRO ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-10 and 12-20* is/are pending in the application.

4a) Of the above claim(s) *1-3,7-10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 9/11/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 9/11/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for screening for a substance which improves endothelial functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims**.

5. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

6. **Nature of the invention and Breadth of the Claims**: The instant invention is drawn to a method of screening for a substance which improves endothelial functions, which comprises labeling a Rac protein in a HUVEC, adding a test substance to a said HUVEC, and measuring (15 hours after addition of said test substance, as recited by instant claim 16) the transfer of Rac protein into the nucleus of said HUVEC (claim 13), more specifically wherein the Rac protein is in the form of a fusion protein which includes a fluorescent protein (claim 14) and/or wherein the transfer of labeled Rac protein into the nucleus is measured by observation with fluorescence (claim 15). As such, the nature of the invention is complex in that it provides for a method of identifying substances which improve endothelial functions. Furthermore, the claims are broad in that they encompass a method for screening for a substance which improves endothelial functions by adding a test substance to a HUVEC and measuring the transfer of Rac protein into the nucleus. As such, the claims are extremely broad in that **any** test substance can be added and screened for its ability to improve **any** endothelial function. Furthermore, the claims are broad in that the method involves measuring the transfer of Rac protein into the nucleus but does not specify the amount of Rac protein transfer to the nucleus that must be measured to indicate that the test compound is capable of being used to improve said functions. Thus, the breadth of the claims is extreme broad, which further exacerbates the complexity of the invention.

7. **Guidance of the specification/The existence of working examples**: The amount of direction provided by the Applicant is considered to be determined by the specification and the working examples. In the instant case, Applicant has provided data which allegedly indicate that

Rac protein is transported into the nucleus of HUVECs (Page 14) following treatment with pitavastatin which, as taught by *Masamura et al* (Aterioscler Thromb Vasc Biol 23:512-517, 2003; cited in a previous Action), is an HMG CoA reductase inhibitor useful for the treatment of vascular conditions and disorders (Abstract). However, as discussed in the previous Action, Applicant's data do **not** demonstrate that the observed translocation of Rac into the nucleus is in any way responsible for pitavastatin's therapeutic effects. That is, there is nothing to suggest that the transfer of Rac into the nucleus is necessary for a substance (such as pitavastatin) to improve endothelial function. For example, Applicant does not demonstrate that blocking the transfer of Rac into the nucleus blocks the endothelial-improving effects of pitavastatin so as to indicate that nuclear import of Rac is necessary for pitavastatin's therapeutic effects. Accordingly, it is unclear whether adding any other test substance to a HUVEC and measuring the transfer of Rac protein into the nucleus would in any way indicate that the test substance is capable of improving endothelial function as recited by instant claims.

8. Applicant, however, argues that *Masamura et al* demonstrate that the inhibition of Rac activity results in improvement of endothelial functions (Applicant Argument, Page 11) and point to the instant Specification which demonstrates that, while Rac protein is normally distributed throughout the cytosol, the addition of pitavastatin promotes transfer of the Rac protein into the nucleus (Applicant Argument, Page 11). As such, Applicant concludes that "the Rac protein loses its activity within the cell, resulting in the improvement of endothelial functions" (Applicant Argument, Page 11). That is, that "one having ordinary skill in the art would understand that the transfer of the Rac protein into the nucleus is responsible for pitavastatin's therapeutic effects" (Applicant Argument, Page 13). Yet, Applicant's arguments

do not overcome the instant rejection. While it is not disputed that inhibition of Rac protein promotes thrombomoduin expression (like pitavastatin) or that pitavastatin promotes translocation of Rac protein into the nucleus, Applicant has not provided any evidence to suggest that said translocation is, in fact, responsible for the inactivation of Rac protein or the improvement of endothelial function as asserted. As previously discussed, and reiterated above, a simple experiment to confirm the role of nuclear Rac translocation in mediating pitavastatin's actions would be to block the uptake of Rac into the nucleus and evaluate whether said blockade inhibits the ability of pitavastatin to improve endothelial function. However, in the absence of such data, it is unclear whether nuclear translocation of Rac protein is critical to the activity of pitavastatin. As such, it is unclear whether any ***other*** test substance that promotes the translocation of Rac protein into the nucleus would improve endothelial function.

9. Furthermore, even assuming *arguendo* that the ability of a test substance to promote Rac protein transfer to the nucleus ***did*** indicate that the test substance could improve endothelial function, the specification does not provide guidance as to the amount of Rac protein which must be transfered into the nucleus. That is, the skilled artisan would not be able to determine (based on Applicant's specification) whether a test substance that increases nuclear Rac levels by 0.00001% (based on increased fluorescence) would be capable of being used to improve endothelial function, or whether more Rac protein must be transferred into the nucleus for the test substance to be effective.

10. Applicant argues that "[i]f the transfer of Rac protein into nucleus has been visually identified, the test substance is thus proved to be a substance which improves endothelial functions" (Applicant Argument, Page 12). Applicant's argument is not considered persuasive.

Even *assuming arguendo* that the nuclear transfer of Rac protein ***does***, in fact, inactivate Rac protein and thus improve endothelial function, if a test substance promoted only a very small amount of Rac protein to be translocated into the nucleus while the overwhelming majority of Rac protein remained in the cytosol, it is unpredictable whether said translocation would, in fact, improve endothelial function.

11. **State of the art/Predictability of the art**: The level of predictability in the art is considered to be relatively low.

12. **Amount of experimentation necessary**: Given the complex nature of the invention, which is exacerbated by the breadth of the claims, and given the lack of working examples and the high degree of unpredictability in the art, it would require undue experimentation for a person of ordinary skill in the art to use the invention as claimed. Since any compound that promotes any transfer of Rac protein into the nucleus would qualify as an agent capable of improving any endothelilal function according to the instant method (and further, considering there is no demonstrated connection between Rac nuclear transport and endothelial function improving ability), it would require undue experimentation to identify which of the test compounds are actually capable of being used to improve endothelial function.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. **Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Furuno et al* (J Immunol 166:4416-4421, 2001) and *Shashidharan et al* (Neuro Report, 10:1149-1153, 1999; Abstract Only).**

16. New claims 17-20 are drawn to a method of screening for a substance that promotes nuclear transfer of a protein, said method comprising labeling a Rac protein in a HUVEC, adding a test substance to a said HUVEC, and measuring (15 hours after addition of said test substance, as recited by instant claim 20) the transfer of Rac protein into the nucleus of said HUVEC (claim 17), more specifically wherein the Rac protein is in the form of a fusion protein which includes a fluorescent protein (claim 18) and/or wherein the transfer of labeled Rac protein into the nucleus is measured by observation with fluorescence (claim 17).

17. Methods for monitoring the nuclear uptake of proteins are well known in the art. In particular, *Furuno et al* disclose methods for monitoring ERK2 (extracellular signal-related kinase 2) translocation into the nucleus of a ERK2-expressing cell comprising labeling said protein with GFP (green fluorescent protein) (which encompasses a fusion protein which includes a fluorescent protein) and measuring the transfer of the labeled protein into the nucleus

by observation with fluorescence (Abstract). Similarly, *Shashidharan et al* disclose methods for monitoring GAPDH (glyceraldehyde-3-phosphate dehydrogenase) translocation into the nucleus using a GAPDH-GFP fusion protein and monitoring its transfer into the nucleus by observation with fluorescence in response to an insult that causes apoptosis.

18. Although neither *Furuno et al* nor *Shashidharan et al* disclose methods for screening for a substance that promotes nuclear transfer of a protein, wherein the method comprises labeling a **Rac protein** in **HUVEC**, it would have been *prima facie* obvious to a person of ordinary skill in the art desiring to investigate the nuclear translocation of Rac protein in said cell to apply the teachings of *Furuno et al* and/or *Shashidharan et al* to said protein in said cell. The skilled artisan would have found it *prima facie* obvious to label a Rac protein in HUVEC (wherein the Rac protein is in the form of a fusion protein which includes a fluorescent protein) and monitor the transfer of labeled Rac protein into the nucleus by observation with fluorescence in view of *Furuno et al* and/or *Shashidharan et al* with a reasonable expectation of success. The skilled artisan would have realized that the methodology disclosed by *Furuno et al* and/or *Shashidharan et al* could be used to identify whether other proteins in other cells are transferred to the nucleus in response to other insults or test substances with a reasonable expectation of success.

19. As such, new claims 17-19 are rejected as prima facie obvious.

20. As to new claim 20, as argued by Applicant, "the period of time over which the HUVEC should be monitored for Rac transfer depends on the culture condition of the HUVEC. This can be suitably determined by one having ordinary skill in the art" and that "the approximate stimulus-response time in HUVEC is well known among those skilled in the art. As such, the time period for the claimed embodiments could have readily been determined in accordance with

the common knowledge in the art, without requiring undue experimentation" (Applicant Argument, Page 12). In view of the foregoing, it is asserted that the skilled artisan would have found it *prima facie* obvious to measure the transfer of labeled Rac protein into the nucleus by observation with fluorescence 15 hours after addition of the test substance based on the culture condition of the HUVEC, the well known stimulus-response time in HUVEC and common knowledge in the art. Accordingly, instant claim 20 is also rejected as *prima facie* obvious.

Conclusion

The new ground(s) of rejection presented in this Office action are necessitated by Applicant's amendments to the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The

examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642